







INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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- (75) Inventors/Applicants (for US only): DUDLEY, David, Thomas [US/US], 3700 Waters Road, Ann Arbor, MI 48103 (US). FLORY, Craig, Mason [US/US]; 3448 Pineview Drive West, Dexter, MI 48130 (US). SALTIEL, Alan, Robert [US/US]; 2002 Valley View Drive, Ann Arbor, MI 48105 (US).
- (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: TREATMENT OF ARTHRITIS WITH MEK INHIBITORS

(57) Abstract

This invention provides a method for preventing and treating arthritis in a mammal suffering from arthritis and in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a MEK inhibitor, including a compound of Formula (I) and Formula (II).

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PCT



(PCT Article 36 and Rule 70)

Applicant		antia fila safaransa					
Applicant's or agent's file reference PD-5968-01-EDS FOR FURTHER ACTIO			FOR FURTHER ACTION		cation of Transmittal of International y Examination Report (Form PCT/IPEA/416)		
International application No.		lication No.	International filing date (day/mo	nth/year)	Priority date (day/month/year)		
PCT/US	99/29	9783	15/12/1999		16/12/1998		
Internation A61K31		ent Classification (IPC) or na	tional classification and IPC				
1 '	R-LA	MBERT COMPANY et	al.				
1. This and i	intern s tran	ational preliminary exami smitted to the applicant a	nation report has been prepar eccording to Article 36.	ed by this Inte	ernational Preliminary Examining Authority		
2. This	REPO	ORT consists of a total of	8 sheets, including this cover	sheet.			
] t	een a	mended and are the bas	d by ANNEXES, i.e. sheets of is for this report and/or sheets or of the Administrative Instruc	containing re	n, claims and/or drawings which have ectifications made before this Authority ne PCT).		
Thes	e ann	exes consist of a total of	sheets.	_			
3. This	report	contains indications relat	ting to the following items:				
ı	\boxtimes	Basis of the report					
н		Priority					
Ш	\boxtimes	Non-establishment of or	pinion with regard to novelty, in	nventive step	and industrial applicability		
IV		Lack of unity of invention					
V	×	Reasoned statement un citations and explanation	der Article 35(2) with regard to ns suporting such statement	novelty, inve	entive step or industrial applicability;		
VI	\boxtimes	Certain documents cited					
VII	\boxtimes	Certain defects in the int	ternational application				
VIII	\boxtimes	Certain observations on	the international application				
Date of sub	missio	n of the demand	Date o	f completion of	this report		
16/06/20	00		14.12.	2000			
	exami	address of the international ning authority:	Author	zed officer	JEPHEDES MICHAE		
<u>@</u>)	D-80	pean Patent Office 298 Munich +49 89 2399 - 0 Tx: 523656 (epmu d Wing	er, R	West of the state		
	Fax:	+49 89 2399 - 4465	Telenh	one No. +49.89	2399 8129		

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

l.	Basis	of the	report
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1.	res the	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).): Description, pages:						
	1-8	1	as originally filed					
	Cla	ims, No.:						
	1-1	6	as originally filed					
2.			juage, all the elements marked above were available or furnished to this Authority in the international application was filed, unless otherwise indicated under this item.					
	The	ese elements were a	available or furnished to this Authority in the following language: , which is:					
		the language of a	translation furnished for the purposes of the international search (under Rule 23.1(b)).					
		the language of pu	ublication of the international application (under Rule 48.3(b)).					
		the language of a 55.2 and/or 55.3).	translation furnished for the purposes of international preliminary examination (under Rule					
3.			leotide and/or amino acid sequence disclosed in the international application, the y examination was carried out on the basis of the sequence listing:					
		contained in the in	ternational application in written form.					
		filed together with	the international application in computer readable form.					
		furnished subsequ	ently to this Authority in written form.					
		furnished subsequ	ently to this Authority in computer readable form.					
		The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.						
		The statement that listing has been full	t the information recorded in computer readable form is identical to the written sequence rnished.					
4.	The	amendments have	resulted in the cancellation of:					
		the description,	pages:					
		the claims,	Nos.:					
		the drawings,	sheets:					
5.			en established as if (some of) the amendments had not been made, since they have been eyond the disclosure as filed (Rule 70.2(c)):					

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/US99/29783

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this

		report.)		g	to an analysis and an analysis
6.	Ado	ditional observations, if n	ecessa	ry:	
III.	. No	n-establishment of opir	nion wit	th regard	d to novelty, inventive step and industrial applicability
		estions whether the clai e industrially applicable t			ppears to be novel, to involve an inventive step (to be non-obvious), xamined in respect of:
		the entire international	applicat	ion.	
	×	claims Nos. 1-16.			
be	caus	se:			
	☒				said claims Nos. 1-16 (industrial applicability) relate to the following n international preliminary examination (<i>specify</i>):
		the description, claims of that no meaningful opin			icate particular elements below) or said claims Nos. are so unclear med (specify):
		the claims, or said claim could be formed.	ns Nos.	are so ir	nadequately supported by the description that no meaningful opinion
		no international search	report h	as been	established for the said claims Nos
2.	and				ination report cannot be carried out due to the failure of the nucleotid y with the standard provided for in Annex C of the Administrative
		the written form has not	been fu	urnished (or does not comply with the standard.
					en furnished or does not comply with the standard.
V.		soned statement unde tions and explanations			vith regard to novelty, inventive step or industrial applicability; ch statement
1.	Stat	ement			
	Nov	elty (N)	Yes: No:	Claims Claims	
	Inve	ntive step (IS)	Yes: No:	Claims Claims	1-16
	Indu	strial applicability (IA)	Yes:	Claims	see section III

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

No: Claims

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

EXAMINATION REPORT - SEPARATE SHEET

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-16 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Prior Art: Reference is made to the following documents cited in the International 2. Search Report

D1: WO 99 61440 A

D2: WO 99 57101 A

D3: WO 99 01449 A

D4: J. BIOL. CHEM., vol. 273 (1998), pages 24832-24838

D5: J. PHARM. EXP. THERAP., vol. 284 (1998), pages 687-692

D6: J. OF IMMUNOLOGY, vol. 161 (1998), pages 467-473

D7: WO 98 37881 A: cited in the application

D8: BIOORG. MED. CHEM. LETT., vol. 8 (1998), pages 3335-3340

D9: WO 98 28292 A

D10: WO 96 00082 A

- 3. Novelty and Inventive Step (Article 33(2) and (3) PCT):
- 3.1 Claims 1-5 relate to the treatment/prevention of arthritis comprising administering an effective antiarthritic amount of a MEK inhibitor.

Documents D4-D6 and D8-D9, which disclose imidazole and indole derivatives, respectively, acting as p38-MAPK inhibitors for the treatment of arthritis, do not seem to anticipate the subject-matter of claims 1-5.

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Document D10, however, discloses the use of bromelain, which inhibits the phosphorylation of MAPK (p 31), for the treatment of rheumatoid arthritis (claim 15). thus anticipating the subject-matter of claims 1-5, which is therefore not novel.

Besides, taking into account that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis (cf. documents D4-D6, D8-D9), the choice to inhibit the "upstream" kinase does not seem to involve an inventive step.

3.2 Claims 6-14 and 15-16 relate to the treatment/prevention of arthritis using specific MEK inhibitors/compounds.

Documents D4-D6 and D8-D9, disclose imidazole and indole derivatives, respectively, as MAPK inhibitors for the treatment of arthritis, thus differing with respect to the compounds used. Accordingly, the subject-matter of said claims seems to be novel.

The problem to be solved by the current application can be regarded as to provide alternative compounds for the treatment of arthritis.

Taking into account that document D7 discloses the same compounds as MEK inhibitors (for the treatment of sceptic shock) and that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis, the subject-matter of claims 6-16 does not seem to be inventive.

4. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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EXAMINATION REPORT - SEPARATE SHEET

Re Section VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/year)
D1: WO 99 61440 A	02.12.99	25.05.99	26.05.98
D2: WO 99 57101 A	11.11.99	28.04.99	05.05.98 and 02.03.99
D3: WO 99 01449 A	14.01.99	26.06.98	30.06.97

5. Document D1 could anticipate the novelty of claims 1-5 in the regional phase.

Re Section VII

Certain defects in the international application

- 6. On page 52, the name for example 207 seems to be wrong.
- 7. The chemical name of PD 199601 on page 77 in Table 3 seems to be missing.
- 8. The second concentration of PD 184352 in Table 4 on page 78 seems to be wrong.

Re Section VIII

Certain observations on the international application

- 9. Independent claim 1 (and dependent claims) do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (MEK inhibitor) which merely amounts to a statement of the underlying problem. It is not clear which criterium (e.g., IC₅₀-test) has to be met for a compound to fall within the scope of the claim.
- 10. The parentheses in claim 6 for the definition of Z being hetero-cycloalkyl seem to be wrong.
- The sulfamoyl-substituted compounds of dependent claim 7 do not seem to fall within 11. the range of Formula I (claim 6).

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EXAMINATION REPORT - SEPARATE SHEET

- Claim 8 seems to be unclear ("or (k) or combinations of the above").
- 13. The compound 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2ylmethoxy)-benzamide in claim 13 (p 98) seems to be wrong.
- The PD-number of the last compound in claim 14 is missing.
- 15. The embodiments of the invention "synthesis and synthetic intermediates" described on page 24, line 15, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- 16. The embodiments of the invention "thiobenzoic acid" described on page 47, examples 140-145, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- The vague statement "scope" of the specification used on page 35 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret it (PCT-Guidelines, III-4.3a).

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



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PCT

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- (21) International Application Number: PCT/US99/29783
- (74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 et al. (US).

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 - 15 December 1999 (15.12.1999)
- (81) Designated States (national): AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA.

(25) Filing Language:

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60/112,544 60/164,651 16 December 1998 (16.12.1998) US 10 November 1999 (10.11.1999) US (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

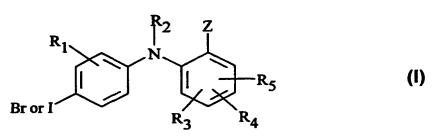
Published:

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- (72) Inventors; and
- (75) Inventors/Applicants (for US only): DUDLEY, David, Thomas [US/US]; 3700 Waters Road, Ann Arbor, MI 48103 (US). FLORY, Craig, Mason [US/US]; 3448 Pineview Drive West, Dexter, MI 48130 (US). SALTIEL,
- (88) Date of publication of the international search report: 18 October 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: TREATMENT OF ARTHRITIS WITH MEK INHIBITORS



(57) Abstract: This invention provides a method for preventing and treating arthritis in a mammal suffering from arthritis and in need of treatment, or suspected of developing arthritis, said method comprising the step of administering an effective antiarthritic amount of a MEK inhibitor, including a compound of Formula (I) and Formula (II).



00/35436 A3

Inte onal Application No PCT/US 99/29783

A. CLASSIF IPC 7	A61K31/195 A61K31/166 A6 A61K31/495 A61K31/535 A6	51K31/136 51K31/38	A61K31/41 A61K31/34	A61K31/445		
According to	International Patent Classification (IPC) or to both natio	nal classification an	d IPC			
	SEARCHED					
Minimum do	cumentation searched (classification system followed by A61K	y classification symi	bols)			
Documentat	ion searched other than minimum documentation to the	extent that such do	cuments are included in	n the fields searched		
Electronic da	ata base consulted during the international search (nam	e of data base and,	where practical, searc	h terms used)		
	THIS CONSIDERED TO BE RELEVANT					
	etion of document, with indication, where appropria	ate, of the relevant p	passages	Relevant to claim No.		
Р	WO 99 61440 A (SMITHKLINE 2 December 1999 (1999-12-0 claims 1-8)	1–5		
	WO 99 57101 A (F. HOFFMANN 11 November 1999 (1999-11- page 52, line 14 - line 23 claims 1,37-43	11)	AG)	1-5		
	WO 99 01449 A (NOVARTIS AG 14 January 1999 (1999-01-1 claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24,	4)		1-5		
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1						
Fur	ther documents are listed in the continuation of box C.	X	Patent family memb	ers are listed in annex.		
Special c	ategories of cited documents :	"T" la	ler document nublished	after the international filing date		
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which	cate ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another on or other special reason (as specified)	ovel or cannot be considered to when the document is taken alone levance; the claimed invention				
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other means ments, such combination being obvious to a person skilled in the art. "P" document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family						
	actual completion of the international search		Date of mailing of the int	ernational search report		
,	5 April 2000		19/04/2000	3003		
Name and	mailing address of the ISA		uthorized officer			
	European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Siatou, E			

Inte Jonal Application No
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·		PC1/US 99/29/83
C.(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XPOO2134930 abstract	1-5
Y	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Y	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5
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Intic Jonal Application No PCT/US 99/29783

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	Relevant to daim No.
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to daim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19	1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21	1-5
Α	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document	1-16
		·

...iernational application No.

PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 1-16 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box il Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

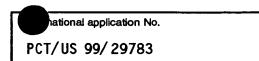
in. itional Application No PCT/US 99/29783

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9961440 A	02-12-1999	NONE	
WO 9957101 A	11-11-1999	NONE	
WO 9901449 A	14-01-1999	AU 8801598 A NO 996429 A ZA 9805656 A	25-01-1999 23-12-1999 30-12-1998
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WO 9828292 A	02-07-1998	NONE	
WO 9600082 A	04-01-1996	AU 2749395 A CA 2193654 A CN 1151119 A EP 0766565 A FI 965204 A JP 10502073 T NO 965564 A	19-01-1996 04-01-1996 04-06-1997 09-04-1997 21-02-1997 24-02-1998 24-02-1997
US 5525625 A	11-06-1996	AT 181913 T AU 690400 B AU 4245696 A CA 2208075 A DE 69510696 D DE 69510696 T EP 0805807 A GR 3031295 T JP 10512878 T NZ 297320 A WO 9622985 A ZA 9600528 A	15-07-1999 23-04-1998 14-08-1996 01-08-1996 12-08-1999 23-12-1999 12-11-1997 31-12-1999 08-12-1998 28-05-1999 01-08-1996 15-08-1996

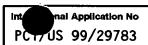
(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 bell ACTION						
International application No. International filing date (day/month/year) (Earliest) Priority Date (day/month/year)						
PCT/US 99/29783	15/12/1999	16/12/1998				
Applicant						
WARNER-LAMBERT COMPANY et	al.					
This International Search Report has been according to Article 18. A copy is being to	n prepared by this International Searching A ansmitted to the International Bureau.	uthority and is transmitted to the applicant				
This International Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in the	nis report.				
Basis of the report						
	international search was carried out on the I ess otherwise indicated under this item.	pasis of the international application in the				
the international search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of	f the international application furnished to this				
was carried out on the basis of the	e sequence listing:	international application, the international search				
	onal application in written form. Imational application in computer readable f	orm				
	this Authority in written form.	orni.				
	this Authority in computer readble form.					
the statement that the sul	osequently furnished written sequence listing is filed has been furnished.	g does not go beyond the disclosure in the				
l —		n is identical to the written sequence listing has been				
2. X Certain claims were fou	nd unsearchable (See Box I).					
3. Unity of invention is lac	king (see Box II).					
4. With regard to the title ,						
The text is approved as su	bmitted by the applicant.					
the text has been established by this Authority to read as follows:						
5. With regard to the abstract,						
the text is approved as su	ibmitted by the applicant.					
the text has been establis	,	ority as it appears in Box III. The applicant may, report, submit comments to this Authority.				
6. The figure of the drawings to be pub	lished with the abstract is Figure No.					
as suggested by the appl	icant.	None of the figures.				
because the applicant fail	ed to suggest a figure.					
because this figure better	characterizes the invention.					





Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.:
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.



A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/195 A61K31/166

A61K31/495

A61K31/535

A61K31/136 A61K31/38

A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) $\begin{tabular}{ll} IPC & 7 & A61K \end{tabular}$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
	- Property of the second of th		
X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5	
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5	
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14	1-5	

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the International filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search 5 April 2000	Date of mailing of the international search report 19/04/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Siatou, E



Int Phase Application No PC17US 99/29783

	FC1/03 99/29/83
	Relevant to daim No.
Chairds of document, with indicators, whole appropriate, or the televant passages	Toovan to dam 170.
K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
page 24837, right-hand column, last paragraph	6-16
J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XPO02134931	1-5
abstract page 690, right-hand column, line 7 - line 24	6-16
A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932	1-5
page 472, right-hand column, last paragraph	6-16
WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5
	Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract page 24837, right-hand column, last paragraph J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931 abstract page 690, right-hand column, line 7 - line 24 A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract page 472, right-hand column, last paragraph WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9 HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2



nal Application No PC1, JS 99/29783

	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	la i
tegory °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19	1-5
(WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21	1-5
\	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document	1-16
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INTERNATIONAL SEARCH REPORT Information patent family members

Int an nai Application No
PC1, US 99/29783

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	tent document I in search report		Publication date		atent family member(s)		Publication date
WO	9961440	Α	02-12-1999	NONE			
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				FI	96520		21-02-1997
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US	5525625	Α	11-06-1996	AT	18191		15-07-1999
				AU	69040		23-04-1998
				AU	424569		14-08-1996
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				DE	6951069		23-12-1999
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				NZ	29732		28-05-1999
				WO	962298		01-08-1996
				ZA	960052	BA	15-08-1996



PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification o	of Transmittal of International Search Report
5968-01-EDS	ACTION (Form PCT/ISA/2)	20) as well as, where applicable, item 5 below.
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 99/29783	15/12/1999	16/12/1998
Applicant		
WARNER-LAMBERT COMPANY et	al.	
This International Search Report has beer according to Article 18. A copy is being tra	n prepared by this International Searching Auth ansmitted to the International Bureau.	nority and is transmitted to the applicant
This International Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in this	report.
Basis of the report		
a. With regard to the language, the i	international search was carried out on the bas ess otherwise indicated under this item.	sis of the international application in the
the international search was Authority (Rule 23.1(b)).	as carried out on the basis of a translation of th	ne international application furnished to this
b. With regard to any nucleotide and was carried out on the basis of the	d/or amino acid sequence disclosed in the in-	ternational application, the international search
	nal application in written form.	
filed together with the inte-	rnational application in computer readable form	n.
furnished subsequently to	this Authority in written form.	
furnished subsequently to	this Authority in computer readble form.	
the statement that the sub international application as	sequently furnished written sequence listing do s filed has been furnished.	pes not go beyond the disclosure in the
		identical to the written sequence listing has been
2. X Certain claims were four	nd unsearchable (See Box I).	
3. Unity of invention is lack	ding (see Box II).	
4. With regard to the title,		
X the text is approved as sub	bmitted by the applicant.	
	hed by this Authority to read as follows:	
•		
5. With regard to the abstract,		
the text is approved as sub- the text has been establish within one month from the	bmitted by the applicant. ned, according to Rule 38.2(b), by this Authority date of mailing of this international search repo	y as it appears in Box III. The applicant may, ort, submit comments to this Authority.
6. The figure of the drawings to be published	shed with the abstract is Figure No.	
as suggested by the applic	ant.	None of the figures.
because the applicant faile	d to suggest a figure.	
because this figure better o	characterizes the invention.	



rnational application No.

PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: 1-16 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.



A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/166

A61K31/495

A61K31/535

A61K31/136 A61K31/38

A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT			
Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5		
WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5		
WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14	1-5		
	W0 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8 W0 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43 W0 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14		

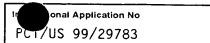
χ Further documents are listed in the continuation of box C.	χ Patent family members are listed in annex.
 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search 5 April 2000	Date of mailing of the international search report $19/04/2000$
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2	Authorized officer
NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Siatou, E





C.(Continu	lation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5
Υ	page 24837, right-hand column, last paragraph	6-16
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5
Y	abstract page 690, right-hand column, line 7 - line 24	6-16
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5
Υ	page 472, right-hand column, last paragraph	6-16
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5





		PC1/US 99	
	C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT Category Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.		
category °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19		1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21		1-5
	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document		1-16

n on patent family members

i ional Application No PCT/US 99/29783

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Patent document cited in search report		Publication date	ſ	Patent family member(s)		Publication date
WO 9961440	Α	02-12-1999	NONE			
WO 9957101	Α	11-11-1999	NONE	:		
WO 9901449	Α	14-01-1999	AU NO ZA	8801598 996429 9805656	Α	25-01-1999 23-12-1999 30-12-1998
W0 9837881	Α	03-09-1998	 AU ZA	5610398 9801578	 А	18-09-1998 02-09-1998
W0 9828292	Α	02-07-1998	NONE			
WO 9600082	A	04-01-1996	AU CA CN EP FI JP NO	2749395 2193654 1151119 0766565 965204 10502073 965564	A A A T	19-01-1996 04-01-1996 04-06-1997 09-04-1997 21-02-1997 24-02-1998 24-02-1997
US 5525625	A	11-06-1996	AT AU CA DE DE EP GR JP NZ WO ZA	181913 690400 4245696 2208075 69510696 69510696 0805807 3031295 10512878 297320 9622985 9600528	B A A D T A T T A A	15-07-1999 23-04-1998 14-08-1996 01-08-1996 12-08-1999 23-12-1999 12-11-1997 31-12-1999 08-12-1998 28-05-1999 01-08-1996 15-08-1996



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS		of Transmittal of International Search Report 220) as well as, where applicable, item 5 below.					
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)					
PCT/US 99/29783 15/12/1999 16/12/1998							
Applicant WARNER-LAMBERT COMPANY et	al.						
This International Search Report has bee according to Article 18. A copy is being tra	n prepared by this International Searching Auti ansmitted to the International Bureau.	hority and is transmitted to the applicant					
This International Search Report consists It is also accompanied by	of a total of sheets. a copy of each prior art document cited in this	report.					
Basis of the report a. With regard to the language, the	international search was carried out on the ba	sis of the international application in the					
	ess otherwise indicated under this item.						
the international search w Authority (Rule 23.1(b)).	as carried out on the basis of a translation of t	he international application furnished to this					
b. With regard to any nucleotide an was carried out on the basis of the		nternational application, the international search					
	onal application in written form.						
filed together with the inte	filed together with the international application in computer readable form.						
furnished subsequently to	furnished subsequently to this Authority in written form.						
furnished subsequently to	furnished subsequently to this Authority in computer readble form.						
	osequently furnished written sequence listing d s filed has been furnished.	loes not go beyond the disclosure in the					
		s identical to the written sequence listing has been					
2. X Certain claims were fou	nd unsearchable (See Box I).						
3. Unity of invention is lac	king (see Box II).						
4. With regard to the title,							
X the text is approved as su	bmitted by the applicant.	•					
the text has been establis	hed by this Authority to read as follows:						
E. With report to the physics							
5. With regard to the abstract.							
5. With regard to the abstract, the text is approved as su	bmitted by the applicant.						
the text is approved as su	bmitted by the applicant. hed, according to Rule 38.2(b), by this Authori date of mailing of this international search rep						
the text is approved as su the text has been establis	hed, according to Rule 38.2(b), by this Authoric date of mailing of this international search rep						
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the text is approved as su the text has been establis within one month from the	hed, according to Rule 38.2(b), by this Authoric date of mailing of this international search replished with the abstract is Figure No.	oort, submit comments to this Authority.					



ernational application No.
PCT/US 99/29783

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
 X Claims Nos.: 1-16 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically: 3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Remark on Protest The additional search fees were accompanied by the applicant's protest.
The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.



A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/166

A61K31/495

A61K31/535

A61K31/136 A61K31/38

A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

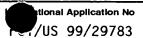
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVAN					
Category °	Citation of document, with indication, wh				

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Х,Р	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1-5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14	1-5

Y Further documents are listed in the continuation of box C.	χ Patent family members are listed in annex.
 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filling date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	 "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search	Date of mailing of the international search report
5 April 2000	19/04/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Siatou, E



		167/US 99/29/83			
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT					
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
X	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5			
Υ	page 24837, right-hand column, last paragraph	6-16			
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5			
Y	abstract page 690, right-hand column, line 7 - line 24	6-16			
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932 abstract	1-5			
Y	page 472, right-hand column, last paragraph	6-16			
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16			
X	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, GB, OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5			



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	ation) DOCUMENTS CONSIDERED TO BE RELEVANT		Industrial in
ategory °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.
(WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19		1-5
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21		1-5
	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document		1-16
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P. ENT COOPERATION TREA.

	From the INTERNATIONAL BUREAU
PCT	То:
NOTIFICATION OF ELECTION (PCT Rule 61.2) Date of mailing (day/month/year) 16 August 2000 (16.08.00)	Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE
International application No.	Applicant's or agent's file reference
PCT/US99/29783	5968-01-EDS
International filing date (day/month/year) 15 December 1999 (15.12.99)	Priority date (day/month/year) 16 December 1998 (16.12.98)
Applicant	
DUDLEY, David, Thomas et al	
The designated Office is hereby notified of its election made in the demand filed with the International Preliminary 16 June 2000 (in a notice effecting later election filed with the International Preliminary 17 The election X was was not was not was not was not was not was not Rule 32.2(b).	y Examining Authority on: (16.06.00) national Bureau on:
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The International Bureau of WIPO	Authorized officer

Form PCT/IB/331 (July 1992)

Facsimile No.: (41-22) 740.14.35

34, chemin des Colombettes 1211 Geneva 20, Switzerland

US9929783

Christelle Croci

Telephone No.: (41-22) 338.83.38

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

WARNER-LAMBERT COMPANY et al.

MANSMANN, I. Patentwesen NOTIFICATION OF TRANSMITTAL OF Warner-Lambert Company Legal Division THE INTERNATIONAL PRELIMINARY Eing.: 15. Dez. 2000 c/o Gödecke AG, Patents **EXAMINATION REPORT** Mooswaldallee 1 (PCT Rule 71.1) D-79090 Freiburg **ALLEMAGNE** Date of mailing (day/month/year) 14.12.2000 right groupers magging Applicant's or agent's file reference IMPORTANT NOTIFICATION PD-5968-01-EDS International filing date (day/month/year) Priority date (day/month/year) International application No. 16/12/1998 15/12/1999 PCT/US99/29783 **Applicant**

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

Authorized officer

European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d

Hundt, D

Fax: +49 89 2399 - 4465

Tel.+49 81



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's o	_	nt's file reference	FOR FURTHER AC	TION See Notif	cation of Transmittal of International ry Examination Report (Form PCT/IPEA/416)
International			international filing date (d	av/month/year)	Priority date (day/month/year)
PCT/US9	• •		15/12/1999	•	16/12/1998
			tional classification and IPC		
A61K31/0		, ,	Single State		
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Applicant			85.50		
1 ''		MBERT COMPANY et	al		
1. This in and is	terna trans	ational preliminary exami emitted to the applicant a	ination report has been paccording to Article 36.	orepared by this in	ternational Preliminary Examining Authority
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2. This R	EPO	RT consists of a total of	8 sheets, including this	COABL 21166F	
п п	nis re	port is also accompanie	d by ANNEXES, i.e. she	ets of the descript	on, claims and/or drawings which have
he	on a	mended and are the bas	is for this report and/or	sheets containing:	rectifications made before this Authority
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"	⊠	Non-establishment of C	pinion with regard to no	velty, inventive ste	p and industrial applicability
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V	×	Reasoned statement u	nder Article 35(2) with re ons suporting such state	gard to novelty, in	ventive step or industrial applicability;
l vi	×	Certain documents cit			
VII	X	Certain defects in the in	nternational application		
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Form PCT/IPEA/409 (cover sheet) (January 1994)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

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		is of the report		
1.	resp the	oonse to an invitation	n under Article 1	s of (substitute sheets which have been furnished to the receiving Office in 14 are referred to in this report as "originally filed" and are not annexed to endments (Rules 70.16 and 70.17).):
		•		
	1-8	1	as originally filed	
	Cla	ims, No.:		
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	1-10	6	as originally filed	
2.	With	n regard to the lang e guage in which the ir	u age, all the elec nternational appl	ments marked above were available or furnished to this Authority in the lication was filed, unless otherwise indicated under this item.
	The	se elements were a	vailable or fumis	shed to this Authority In the following language: , which is:
		the language of a t	ranslation furnisi	hed for the purposes of the international search (under Rule 23.1(b)).
		the language of pul	blication of the ir	nternational application (under Rule 48.3(b)).
		the language of a to 55.2 and/or 55.3).	ranslation fumisl	hed for the purposes of international preliminary examination (under Rule
3.	Witl inte	n regard to any nuc l mational preliminary	leotide and/or a examination wa	amino acid sequence disclosed in the international application, the as carried out on the basis of the sequence listing:
		contained in the int	ernational applic	cation in written form.
		filed together with t	he international	application in computer readable form.
		furnished subseque	ently to this Auth	nority in written form.
		furnished subseque	ently to this Auth	nority in computer readable form.
		The statement that the international ap	the subsequent	tly furnished written sequence listing does not go beyond the disclosure in the disc
		The statement that listing has been fur		recorded in computer readable form is identical to the written sequence
4.	The	amendments have	resulted in the c	ancellation of:
		the description,	pages:	
		the claims,	Nos.:	material section of the section of t
		the drawings,	sheets:	
		···•		
5.		This report has bee	en established å	s if (some of) the amendments had not been made, since they have been

Form PCT/IPEA/409 (Boxes I-VIII, Sheet 1) (July 1998)

considered to go beyond the disclosure as filed (Rule 70.2(c)):





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

		,			
6.	Add	litional observations, if ne	ecessan	y:	
161.	Nor	n-establishment of opin	ion witi	h regard	to novelty, inventive step and industrial applicability
Th	e an		ned inve	ention app	pears to be novel, to involve an inventive step (to be non-obvious),
		the entire international	applicati	on.	
	×	claims Nos. 1-16.			
be	caus	se:		ش	en in 1944 September 1955 September 1955
	Ø	the said international as subject matter which do see separate sheet	oplication bes not r	n, or the s equire an	said claims Nos. 1-16 (industrial applicability) relate to the following international preliminary examination (<i>specify</i>):
		the description, claims that no meaningful opin	or drawi ilon coul	ngs (<i>indic</i> ld be form	cate particular elements below) or said claims Nos. are so unclear ned (specify):
		the claims, or said clain could be formed.	ns Nos.	are so in	nadequately supported by the description that no meaningful opinion
		no international search	report h	as been	established for the said claims Nos
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					or does not comply with the standard. In furnished or does not comply with the standard.
		the computer readable	torm na	s not bee	in turnshed of does not comply with the standard.
V.	Re	asoned statement unde ations and explanations	er Articles 8 suppo	e 35(2) w erting suc	vith regard to novelty, inventive step or industrial applicability; ch statement
1.		tement			
	No	velty (N)	Yes: No:	Claims Claims	
	Inv	entive step (IS)	Yes: No:	Claims Claims	
	Ind	lustrial applicability (IA)	Yes:	Claims	see section III





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/29783

No: Claims

2. Citations and explanations see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

Re Section III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-16 relate to subject-matter considered by this Authority to be covered by the 1. provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Section V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Prior Art: Reference is made to the following documents cited in the International 2. Search Report

D1: WO 99 61440 A

D2: WO 99 57101 A

D3: WO 99 01449 A

D4: J. BIOL. CHEM., vol. 273 (1998), pages 24832-24838

D5: J. PHARM. EXP. THERAP., vol. 284 (1998), pages 687-692

D6: J. OF IMMUNOLOGY, vol. 161 (1998), pages 467-473

D7: WO 98 37881 A: cited in the application

D8: BIOORG. MED. CHEM. LETT., vol. 8 (1998), pages 3335-3340

D9: WO 98 28292 A

D10: WO 96 00082 A

- Novelty and Inventive Step (Article 33(2) and (3) PCT): 3.
- 3.1 Claims 1-5 relate to the treatment/prevention of arthritis comprising administering an effective antiarthritic amount of a MEK inhibitor.

Documents D4-D6 and D8-D9, which disclose imidazole and indole derivatives, respectively, acting as p38-MAPK inhibitors for the treatment of arthritis, do not seem to anticipate the subject-matter of claims 1-5.





INTERNATIONAL PRELIMINARY Inter EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/US99/29783

Document D10, however, discloses the use of bromelain, which inhibits the phosphorylation of MAPK (p 31), for the treatment of rheumatoid arthritis (claim 15), thus anticipating the subject-matter of claims 1-5, which is therefore not novel.

Besides, taking into account that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis (cf. documents D4-D6, D8-D9), the choice to inhibit the "upstream" kinase does not seem to involve an inventive step.

3.2 Claims 6-14 and 15-16 relate to the treatment/prevention of arthritis using specific MEK inhibitors/compounds.

Documents D4-D6 and D8-D9, disclose imidazole and indole derivatives, respectively, as MAPK inhibitors for the treatment of arthritis, thus differing with respect to the compounds used. Accordingly, the subject-matter of said claims seems to be novel.

The problem to be solved by the current application can be regarded as to provide alternative compounds for the treatment of arthritis.

Taking into account that document D7 discloses the same compounds as MEK inhibitors (for the treatment of sceptic shock) and that inhibition of the kinase-cascade seems to be an obvious approach for the treatment of arthritis, the subject-matter of claims 6-16 does not seem to be inventive.

4. Industrial Applicability (Article 33(4) PCT):

For the assessment of the present claims 1-16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.



INTERNATIONAL PRELIMINARY

International application No. PCT/US99/29783

EXAMINATION REPORT - SEPARATE SHEET

Re Section VI

Certain documents cited

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (day/month/year)
D1: WO 99 61440 A	02.12.99	25.05.99	26.05.98
D2: WO 99 57101 A	11.11.99	28.04.99	05.05.98 and 02.03.99
D3: WO 99 01449 A	14.01.99	26.06.98	30.06.97

Document D1 could anticipate the novelty of claims 1-5 in the regional phase. 5.

Re Section VII

Certain defects in the international application

- On page 52, the name for example 207 seems to be wrong. 6.
- The chemical name of PD 199601 on page 77 in Table 3 seems to be missing. 7.
- The second concentration of PD 184352 in Table 4 on page 78 seems to be wrong. 8.

Re Section VIII

Certain observations on the international application

- Independent claim 1 (and dependent claims) do not meet the requirements of Article 9. 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved (MEK inhibitor) which merely amounts to a statement of the underlying problem. It is not clear which criterium (e.g., IC_{50} -test) has to be met for a compound to fall within the scope of the claim.
- 10. The parentheses in claim 6 for the definition of Z being hetero-cycloalkyl seem to be wrong.
- 11. The sulfamoyl-substituted compounds of dependent claim 7 do not seem to fall within the range of Formula I (claim 6).



International application No. PCT/US99/29783

INTERNATIONAL PRELIMINARY Inter EXAMINATION REPORT - SEPARATE SHEET

- 12. Claim 8 seems to be unclear ("or (k) or combinations of the above").
- 13. The compound 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide in claim 13 (p 98) seems to be wrong.
- 14. The PD-number of the last compound in claim 14 is missing.
- 15. The embodiments of the invention "synthesis and synthetic intermediates" described on page 24, line 15, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- 16. The embodiments of the invention "thiobenzoic acid" described on page 47, examples 140-145, do not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- 17. The vague statement "scope" of the specification used on page 35 implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret it (PCT-Guidelines, III-4.3a).

PATENT COOPERATION TR

B. ARMSTRONG

From the INTERNATIONAL SEARCHING AUTHORITY	PCT
UNITED STATES OF AMERICA	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION APR 2 4 2000 (PCT Rule 44.1) PATENT DEPT.
	Date of mailing (day/month/year) 19/04/2000
Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 99/ 29783	International filing date (day/month/year) 15/12/1999
WARNER-LAMBERT COMPANY et al.	
1. X The applicant is hereby notified that the International Search Filing of amendments and statement under Article 19: The applicant is entitled, if he so wishes, to amend the claim When? The time limit for filing such amendments is normal International Search Report; however, for more detailed International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41–22) 740.14.35 For more detailed instructions, see the notes on the account of the applicant is hereby notified that no International Search Article 17(2)(a) to that effect is transmitted herewith.	ns of the International Application (see Rule 46): ally 2 months from the date of transmittal of the stails, see the notes on the accompanying sheet.
	onal fee(s) under Rule 40.2, the applicant is notified that: In transmitted to the international Bureau together with the test and the decision thereon to the designated Offices.
no decision has been made yet on the protest; the app	plicant will be notified as soon as a decision is made.
4. Further action(s): The applicant is reminded of the following:	
Shortly after 18 months from the priority date, the international at if the applicant wishes to avoid or postpone publication, a notice priority claim, must reach the International Bureau as provided completion of the technical preparations for international publications.	e of withdrawal of the international application, or of the in Rules 90 <i>bis</i> .1 and 90 <i>bis</i> .3, respectively, before the ation.
Within 19 months from the priority date, a demand for internation wishes to postpone the entry into the national phase until 30 mo	
Within 20 months from the priority date, the applicant must perforbefore all designated Offices which have not been elected in the priority date or could not be elected because they are not bound	e demand or in a later election within 19 months from the

Name and mailing address of the International Searching Authority

European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Renate Jordan

Form PCT/ISA/220 (July 1998)

Express Mail No.EK651646072US PD-5968-01-SMH

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication. (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Notes to Form PCT/ISA/220 (first sheet) (January 1994)



The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed:
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
 "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
- (Where originally there were 15 claims and after amendment of all claims there are 11): "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
 "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46:4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19; a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

Notes to Form PCT/ISA/220 (second sheet) (January 1994)



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 5968-01-EDS	FOR FURTHER See Notification of (Form PCT/ISA/2	FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.				
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)				
PCT/US 99/29783	15/12/1999	16/12/1998				
Applicant WARNER-LAMBERT COMPANY et	al.					
according to Article 18. A copy is being tra		·				
Basis of the report						
a. With recard to the language, the i	nternational search was carried out on the bar ass otherwise indicated under this item.	sis of the international application in the				
the international search was Authority (Rule 23.1(b)).	as carried out on the basis of a translation of t	ne international application furnished to this				
was carried out on the basis of the contained in the internation filed together with the internation furnished subsequently to the statement that the sub international application as	e sequence listing: nal application in written form. mational application in computer readable form this Authority in written form. this Authority in computer readble form. sequently furnished written sequence listing desired has been furnished.					
Ξ	nd unsearchable (See Box I).					
4. With regard to the title, The text is approved as suithe text has been establish the text has bea						
within one month from the 6. The figure of the drawlings to be publi as suggested by the applicant faile because the applicant faile	ned, according to Rule 38.2(b), by this Authoric date of mailing of this international search rep shed with the abstract is Figure No.					



International application No.

PCT/US 99/29783

DOX I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sneet)
This Inte	emational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: 1-16 because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-16 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged
2.	effects of the compound/composition. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This Inte	emational Searching Authority found multiple inventions in this international application, as follows:
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. 🗌	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark	on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

International Application No PCT/US 99/29783



A CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K31/195 A61K

A61K31/495

Ä61K31/166 A61K31/535 A61K31/136 A61K31/38 A61K31/41 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUM	ENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 61440 A (SMITHKLINE BEECHAM CO) 2 December 1999 (1999-12-02) claims 1-8	1-5
X,P	WO 99 57101 A (F. HOFFMANN-LA ROCHE AG) 11 November 1999 (1999-11-11) page 52, line 14 - line 23 claims 1,37-43	1–5
X,P	WO 99 01449 A (NOVARTIS AG) 14 January 1999 (1999-01-14) claims 1-6,8-11 page 20, line 16 - line 21 page 23, line 14 -page 24, line 14 -/	1-5

Further documents are listed in the continuation of box C.	Patent family members are listed in annex.
Special categories of cited documents: 'A' document defining the general state of the art which is not considered to be of particular relevance 'E' earlier document but published on or after the international filing date 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) 'O' document referring to an oral disclosure, use, exhibition or other means 'P' document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention. "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone. "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
Date of the actual completion of the international search 5 April 2000	Date of mailing of the international search report 19/04/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Siatou, E

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International Application No PCT/US 99/29783

Cords	(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT				
ategory °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
K	K. MIYAZAWA ET AL: "Regulation of Interleukin-1-beta-induced Interleukin-6 Gene Expression in Human Fibroblast-like Synoviocytes by p38 Mitogen-activated Protein Kinase" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 38, 18 September 1998 (1998-09-18), pages 24832-24838, XP002134930 abstract	1-5			
Y	page 24837, right-hand column, last paragraph	6-16			
X	J. R. JACKSON ET AL: "Pharmacological Effects of SB 220025, a Selective Inhibitor of P38 Mitogen-Activated Protein Kinase, in Angiogenesis and Chronic Inflammatory Disease Models" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 284, no. 2, 1998, pages 687-692, XP002134931	1-5			
Y	abstract page 690, right-hand column, line 7 - line 24	6-16			
X	A. M. BADGER ET AL: "SB 203580 Inhibits p38 Mitogen-Activated Protein Kinase, Nitric Oxide Production, and iNducible Nitric Oxide Synthase in Bovine Cartillage-Derived Chondrocytes" THE JOURNAL OF IMMUNOLOGY, vol. 161, 1998, pages 467-473, XP002134932	1-5			
Y	abstract page 472, right-hand column, last paragraph	6-16			
Y	WO 98 37881 A (WARNER LAMBERT COMPANY) 3 September 1998 (1998-09-03) cited in the application claims 1-9	6-16			
x	HENRY J R ET AL: "Potent inhibitors of the map kinase p38" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 23, 1 December 1998 (1998-12-01), pages 3335-3340, XP004143754 ISSN: 0960-894X abstract page 3336; table 1 page 3337; table 2	1-5			
	i				

international Application No PCT/US 99/29783

		PC1/03 99/29/83			
	ntion) DOCUMENTS CONSIDERED TO BE RELEVANT	15.			
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.			
X	WO 98 28292 A (SMITHKLINE BEECHAM CO) 2 July 1998 (1998-07-02) claims 1-12,16-19	1-5			
X	WO 96 00082 A (CORTECS LIMITED) 4 January 1996 (1996-01-04) claims 1-6,12,14,15,20 page 7, line 17 -page 8, line 25 page 11, line 21	1-5			
A	US 5 525 625 A (A. J. BRIDGES ET AL) 11 June 1996 (1996-06-11) cited in the application the whole document	1-16			
		·			
		-			

Information on patent family members

International Application No PCT/US 99/29783

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	nt document search report		Publication date		atent family member(s)		Publication date
WO 9	961440	A	02-12-1999	NONE			
WO 9	957101	A	11-11-1999	NONE			
WO 9	901449	Α	14-01-1999	AU	8801598		25-01-1999
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				ZA	9805656	A	30-12-1998
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				CA	2193654		04-01-1996
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				FI	965204		21-02-1997
				JP	10502073		24-02-1998
				NO NO	965564	Α	24-02-1997
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				AU	690400		23-04-1998
				AU		Α	14-08-1996
				CA		Α	01-08-1996
				DE		D	12-08-1999
				DE	69510696	Ţ	23-12-1999
	•			EP	0805807		12-11-1997
				GR		Ţ	31-12-1999
				JP		Ţ	08-12-1998
				NZ	297320		28-05-1999
				MO	9622985		01-08-1996
				ZA	9600528	Α	15-08-1996